EXPERIC

Inhaled Biologics From Zero

By Justin Lacombe, Ph.D., Chief Scientific Officer, Experic

Overview

The big question for those specializing in the development and manufacturing of inhalation therapies is how to support the complexities presented by biologic molecules.

While small molecule drugs remain very important, biologic therapies continue to represent an increasing portion of the global therapeutic pipeline of product in development. Many of these proteins are not suited to delivery through the gastrointestinal tract due to acidic degradation, paracellular transport mechanisms that exclude larger molecules, and other absorption, distribution, metabolism, and excretion (ADME) issues. The injectable delivery of liquids via syringe and needle, as well as infusion, is the least desired format, though common. These delivery methods place a tremendous burden on the healthcare system and supply chain, which became especially apparent during the pandemic.

As a result, strategies have been implemented to improve the human health supply chain with alternatives to needle and syringe delivery. Inhalation is among these therapies. The U.S. Department of Health and Human Services Division of Research, Innovation, and Ventures, for example, introduced *Beyond the Needle*, an initiative supporting the development of alternative technology for making vaccines easier to administer and more widely available, without the burden of having to store and ship the products at cold or frozen temperatures.

Further emphasizing the importance of this topic, the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) recognized the importance of strategies to develop new delivery methods and held a meeting specifically to begin the discussion of inhaled biologics.

This paper highlights the need for a more comprehensive understanding of strategies for developing biologics for inhalation, manufacturing considerations, and a more detailed regulatory pathway.

The New Class

Discussing biologics for inhalation therapies is complex because they encompass a diverse range of compounds and potential delivery formats. That complexity, or the various combinations of options, may be surprising to many, but is important to understand.

Biologics include a broad range of substances such as DNA, mRNA, oligonucleotides, various proteins (including receptor-binding proteins), enzymes, oligopeptides, and more. They mainly fall into the categories of nucleic acid-based substances and peptide-based substances.

For this review, I will largely focus on nucleic acids and proteins, omitting more complex possibilities such as monoclonal antibodies and CRISPR-based gene editing scenarios which may include multiple protein and nucleic acid-based components.

EXPERIC

Delivery Options

The delivery of inhalation products is an equally complex topic. Delivery methods include:

- Nebulizers
- Nasal liquids
- Dry powder inhalation (DPI)
- Pressurized metered-dose inhalers (pMDIs)
- Nasal systems
- Nasal powders

Considerations

There are many considerations when determining what type of delivery product should be used. For instance, with solid delivery systems, a liquid must be converted into a dry powder before it can be used for inhalation, and there are different ways to create the dry powder. We will explore some of those techniques later.

When dealing with the delivery of nasal liquid formulations, one consideration is that higher doses (i.e., milligram-quantities) of a therapeutic entity will be delivered – rather than the microgram-quantities typically delivered in small molecule products. Meanwhile, there are limitations with pressurized metered-dose inhalers related to the quantity of material that can be delivered due to their metering valve size, with valves as large as 600 microliters but most significantly smaller.

There are a couple of examples of dry powder nasal systems that exist now, but they are still relatively rare.

Additional considerations include the stability of the therapeutic, the reformulation, and the native state of the proteins, particularly when transitioning from liquid to inhalation systems. Sterility is also a concern, particularly with the differences in the sterilization requirements for different inhalation systems. For example, dry powder inhalation systems, pressurized metered-dose inhalers, and dry powder nasal systems don't necessarily need to be sterile, while soft-mist inhalers (SMIs) and nebulizers may require sterile filling or terminal sterilization in the absence of preservatives.

Unique Performance Characteristics

Many of the performance characteristics and standards the industry expects and measures in small molecule orally inhaled and nasal drug products (OINDPs) would remain unchanged when dealing with biologics: for instance, unit dose uniformity. Aerosol particle size distribution is important for all inhaled delivery methods. When dealing with a liquid system, the measurements may also include droplet size and/or dose weight. For MDIs and nasal sprays, the spray pattern and plume geometry remain important.

There are, however, delivery challenges that are specific to the performance of biologics, such as oligonucleotides and proteins which when delivered via inhalation, require careful consideration during development and testing, including potency, aggregation, and fragmentation.

- **Potency:** The concept of potency for biologics differs from small molecules. For biologics, potency often involves complex processes, such as binding of proteins, enzyme reactions, or mRNA synthesizing proteins within cells. Ensuring potency in the context of inhalation is challenging, and may need to be considered in the post-delivery. For example, nebulization systems generate droplets which have liquid/air interfaces that can create denaturation conditions.
- **Aggregation:** Proteins can undergo aggregation, particularly when exposed to certain conditions or during the denaturation process. This can impact the stability and efficacy of the biological product and may also lead to immunological responses.
- **Fragmentation:** Shear stresses during delivery or processing may result in damaging the substance itself. This is a potential concern that would need to be addressed as part of the performance characteristics for inhalation delivery.

EXPERIC

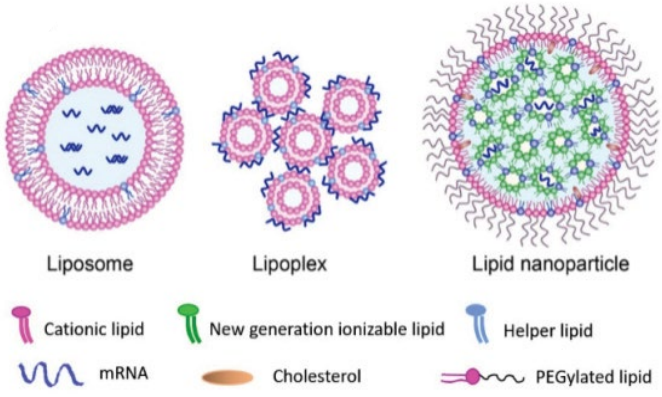
Analytical Challenges

Analyzing a biologic to ensure its quality and performance can be more difficult and extensive than for small molecules. Many techniques may be needed to characterize the products, including dynamic light scattering (DLS), liquid chromatography-mass spectrometry (LCMS), and capillary electrophoresis. These techniques are essential for a sound understanding of the properties of proteins and nucleic acids.

While small molecules are typically characterized using techniques such as reverse-phase HPLC, biologics may require a broader range of characterization methods due to the complexity of proteins, nucleic acids, and lipid nanoparticles used in these products. To comprehensively characterize biologics, it may be necessary to employ multiple orthogonal techniques to assess the product quality attributes and provide different types of information which can help ensure quality and stability.

As with all development programs, these tests should be conducted during development as well as after, with aerosol performance testing to ensure the product's stability and effectiveness post-delivery.

Delivering Nucleic Acids



There are numerous platforms and techniques for the inhalation delivery of nucleic acids, a large class of biologics including RNA. These platforms continue to evolve for optimization.

Some key methods and considerations include:

- **Lipid Nanoparticles:** This is a crucial platform for delivery. The nanoparticles can be employed in different formulations and were used in delivery of the Pfizer COVID-19 vaccine.
- **Naked RNA:** Meaning delivery of RNA without encapsulation in nanoparticles, this is one method of delivering genetic materials.
- **RNA Lipoplexes:** These involve a combination of RNA with lipid-based carriers, potentially enhancing delivery efficiency.
- **Synthetic Surfactants:** These mimic natural lung surfactants and aim to improve compatibility with the lung environment.
- **Additives:** Leucine and others have been explored to enhance the performance of nucleic acid delivery systems.
- **Surfactant-Based Systems:** Components such as 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), and poly lactic-co-glycolic acid (PLGA) nanoparticles have been used as components in delivery systems.

Delivering Proteins

Selecting a delivery system for a protein therapeutic requires careful consideration of its stability, as well as suitable excipients to ensure the effective administration through inhalation or other routes.

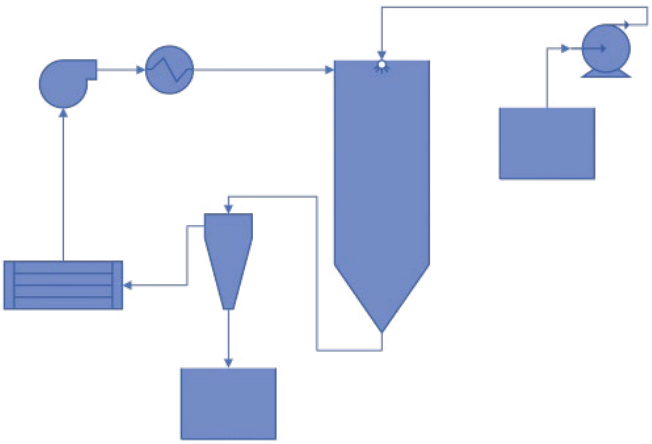
- Stabilizing the protein for delivery is essential and can be achieved using buffers, salts, and sugars.
- Nanoparticles have been employed in protein delivery, likely as carriers to protect and transport them effectively.
- Traditional reducing sugars used in inhalation blends, such as lactose, may not be suitable for these systems due to the risk of shift-based reactions causing protein degradation. Mannitol and sorbitol may be considered possible alternatives.
- PEGylation and the addition of PEG has been used to enhance or optimize the muco-adhesive or muco-penetrative properties of protein delivery systems.

EXPERIC

Creating Dry Powder

There are several methods for creating dry powder for inhalation therapies, including spray drying, spray freeze drying, supercritical precipitation, thin film freezing, and PRINT™ technology. Let's explore a few:

Spray Drying



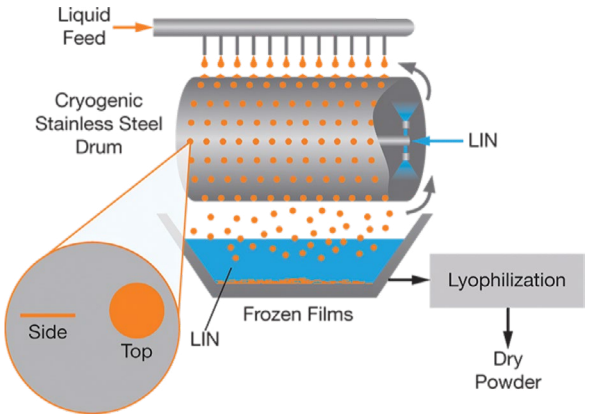
This method for making dry powder offers versatility. It can be used for small molecules as well as biologics.

Spray drying has several advantages including particle size control, which is essential for consistent and effective drug delivery. It can be used to produce large volumes, which makes it a practical choice for pharmaceutical manufacturing.

Spray drying for inhalation biologics is not without its challenges. High temperatures, interfacial surface areas, and shear forces during spray drying can potentially have deleterious effects on some biologics. Large interfacial surface areas may lead to the denaturation of proteins.

Developments in this method of inhalation production include electrostatic spray drying, a technique that involves charging the surface of droplets as they exit the nozzle. The process is designed to drive hydrophobic surface materials to the center of the droplets for more controlled and gentle drying. Its utility for inhalation applications is still being researched.

Thin Film Freezing

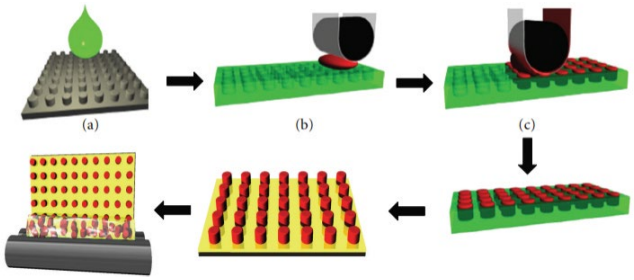


Beteta, O and Ivanova, S. Cool Down with Liquid Nitrogen. CEP (2015), September.

Thin film freezing (TFF) is a low-temperature system in which a liquid feed is dripped onto a cryogenically cooled stainless-steel drum, typically at cryogenic temperatures. It is an intriguing method for dry powder creation but has not yet been used for the manufacture of a commercial product.

- To form powder, the liquid feed forms small discs of material on the cold surface that are subsequently lyophilized to create a powder.
- The powder produced in this process has unique characteristics, including very low density and geometric particle size distributions that are challenging to define. However, they tend to fall within the inhalable range.
- The lyophilization step, which can limit production capacity, has currently occurred at pilot scale. Scale-up of the process will be necessary to make it viable at commercial scale.

EXPERIC



Garcia, A et al. Microfabricated Engineered Particle Systems for Respiratory Drug Delivery and Other Pharmaceutical Applications. Journal of Drug Delivery (2012).

PRINT® (Liquidia)

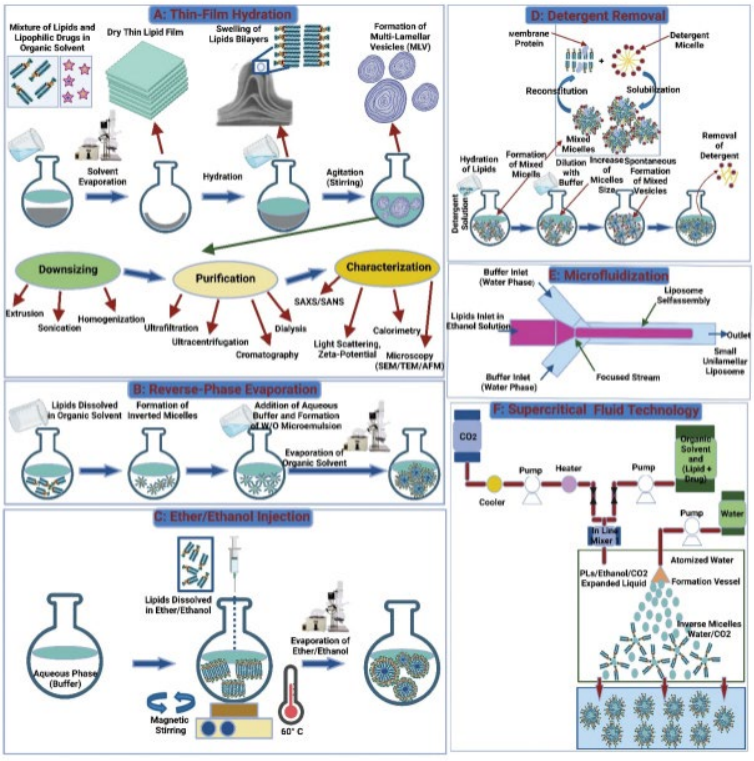
PRINT® is an engineering and manufacturing technology developed and patented by the biopharmaceutical company Liquida, which has used it to develop YUTREPIA™, an inhaled dry powder therapy for pulmonary arterial hypertension.

The process involves creating a template and pressing or flowing the material into the template to form particles. The template plays a crucial role in shaping the particles and its design influences the final particle characteristics.

The technology has the potential to be used for creating particles incorporating proteins and nanoparticles. Its adaptability to different materials makes it promising for a range of applications.

Creating Nanoparticles

Lipid nanoparticles can be created using a range of techniques, with a focus on continuous processes for industrial production. Nanoprecipitation methods, including flash precipitation and electro spray drying, are among the techniques used to form nanoparticles, offering flexibility and scalability in the production of biologics.



Al Japouri et al., Liposomes or Extracellular Vesicles: A Comprehensive Comparison of Both Lipid Bilayer Vesicles for Pulmonary Drug Delivery. Polymers 2023 (15) 318.

EXPERIC

Regulatory Considerations

The U.S. regulatory guidance for biologics delivered via inhalation remains unclear and lacks detailed instructions. The unique challenges of inhalable biologics, including potency evaluation and sterility, are not comprehensively addressed in existing guidelines. Determining the appropriate regulatory pathway for these products is an extremely important consideration.

The existing regulatory guidance for drug-device combination products focuses primarily on the Code of Federal Regulations (CFR) Part 210, which refers to Good Manufacturing Practices (GMP) in the manufacturing, processing, packing, or holding of drugs; section 211, which has more specific guidelines on the manufacturing of pharmaceutical products; and Part 820, known as “Quality System Regulation,” which outlines how to maintain quality for the design, production, and distribution of medical devices. Despite the titles, these guidelines are short on detailed instructions for delivery via inhalation.

Additionally, 21 CFR Part 600 to 680 pertains to biological products but offers little specific guidance on how to address the unique challenges of inhalable biologics compared to small molecule products.

Evaluating the potency of inhalable biologics is also challenging, particularly in distinguishing between in vivo and in vitro tests. The guidance does not offer clear instructions on how to approach the issue.

Sterility is an important consideration for biologics, though guidance mentions exemptions may be granted for inhalable biologics in non-sterile applications. This reflects the limited number of inhalable biologics currently on the market, such as inhaled insulin.

Deciding which regulatory pathway is appropriate for a biologic, whether it is a New Drug Application (NDA), a Biologics License Application (BLA), or involves the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), remains a critical consideration.

Conclusion

Specificity is needed when defining biologics for inhalation because it is a large group of substances, from RNA to oligonucleotides, monoclonal antibodies, and more. Available instrumentation is varied, and it may be challenging to have a comprehensive tool set. Perhaps, strategies will need to be developed on how to analyze each of these categories of biologics consistently.

It appears that many of the manufacturing techniques that are needed to produce inhalation products may already exist in some shape or form, though some reformulation may be necessary.

Meanwhile, the regulatory pathway still lacks specifics and will be staked out in more detail as more of these products go through review for commercialization.

EXPERICSERVICES.COM • 609.537.4040 • 888.397.9733 (toll free) • info@expericservices.com • 2 Clarke Drive, Cranbury, NJ 08512